PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A longitudinal study of occupational noise exposure and joint effects with job-strain and risk for coronary heart disease and stroke in Swedish men
AUTHORS	Eriksson, Helena; Andersson, Eva; Schiöler, Linus; Söderberg, Mia; Sjöström, Mattias; Rosengren, Annika; Torén, Kjell

VERSION 1 – REVIEW

REVIEWER	Ferrario Marco Department of Medicine and Surgery. University of Insubria, Italy
REVIEW RETURNED	19-Aug-2017

GENERAL COMMENTS	This is an interesting research on the joint effect of noise exposure and job strain in increasing the risk of CHD and Stroke. Not many papers addresses this topic and therefore it will be of sure interest for epidemiologists, occupational physicians and cardiologists, I presume. The study is a large prospective follow-up studies conducted by Swedish researchers on a Sweden sample. Both exposures were determined using job-exposure matrices. Results indicate a joint effect between the two exposures for CHD not for stroke. These finding corroborate previous researches' findings of the effects of the two independent exposures, adding more hints on the joint effect. The English is very good and the reader is facilitated in keep reading it. There a few hints I wish to ask the authors to take into account, and that in my understanding may improve the paper. 1. I could not find any indication about the age range on this sample of 5753 working Swedish men. This may tell more about representativeness of the sample; 2. Second para of Introduction: third row, I assume that the term "fatal" needs to be added. Please check; 3. The authors used the same abbreviation for the two job exposure-matrices (page 6). I suggest different acronyms. 4. I could not find a formalized statistical test for interaction. Was it done? On the same issue, looking at Table 3, probably the aggregation of the levels of exposures to noise below and above 75 dB(A), may help in testing the interactions. I also suggest to report the number of subjects and the number of events for each of the cells of Table 3, which may emphases the poor statistical power (which may improved a little with the proposed cell aggregation. 5. Finally, in Discussion first Para of Page 10, I would suggest to emphases the effects of high blood pressure and smoking, in addition to diabetes, which in my knowledge are stronger mediators of the relationships.

REVIEWER	Angel Dzhambov Department of Hygiene and Ecomedicine, Faculty of Public Health, Medical University of Plovdiv, Bulgaria
REVIEW RETURNED	31-Aug-2017

GENERAL COMMENTS	This is a nice piece of research on a subject that is of interest to the occupational health community. Specifically, it adds to the limited body of evidence on occupational noise and stroke. Overall, I enjoyed reading the manuscript. Still, I have some comments that I would like to see addressed before it can be accepted for publication. I regard the necessary revision as "minor" despite the recommend additional analyses. Abstract line 20, Primary and secondary outcome measures: Add ICD codes if possible. line 22: Shouldn't each word in "primary prevention study" be capitalized? line 47: I suggest adding "ischemic heart disease" to the list of keywords. Introduction page 3, lines 5-6, "Exposure to noise is common in many workplaces, and health effects, especially hearing disorders have been investigated since decades.": We sure know this, but a reference should be inserted at the end of the sentence. page 3, line 9: I disagree with the choice of references (№ 1 and 2). First of all, the meta-analysis of Skogstad et al. should be cited along with the erratum to it. You may also check my Letter to the editor concerning the analytical approach of Skogstad et al.. There is reason to suspect that the random effects model in their meta-analysis overestimated the risk of hypertension (which is not to say that there isn't a risk, rather the evidence from cohort studies isn't there yet). Also, you should consider discussing the findings of the following systematic review, dealing with the risk of IHD attributed to occupational noise, in the next paragraph (lines 13-34): Dzhambov AM, Dimitrova DD. Occupational noise and ischemic heart disease: A systematic review. Noise Health. 2016;18(83):167-77. The second and third paragraphs of the Introduction are a bit too detailed for my taste. I would expect to read about previous research and its strengths/limitations in the Discussion, not so early on in the paper. Thus I suggest that you shorten these paragraphs and briefly state what previous research indicated and what gaps still exist in the literature, and cover specific studies in the Discussion. Instead, the Introduction is a good place to briefly mention the epidemiology of CHD and stroke and the burden of disease associated with them, just to put your study in context. also, few notes on the mechanisms linking noise to CVD is worth mentioning.

	The third paragraph, where you talk about previous research on noise and stroke: You have missed two important references that should be mentioned (since there are very few studies on the topic to begin with). The first one reports both cross-sectional and longitudinal associations between noise and CVD, whereas the second one is cross-sectional, population-based study and representative of the US general population. Gopinath B, Thiagalingam A, Teber E, Mitchell P. Exposure to workplace noise and the risk of cardiovascular disease events and mortality among older adults. Prev Med. 2011;53(6):390-4. Dzhambov AM, Dimitrova DD, Tokmakova MP. Association between self-reported occupational noise and the prevalence of stroke: Secondary analysis of the National Health Interview Survey, 2014. Noise Control Engineering Journal. 2016;64(6):779-788. page 4, line 12: I don't see how the interaction between noise and smoking is relevant. Methods page 4, lines 34-35: Consider putting "BMI is the weight in kilograms divided by the square of the body height in meters" in parenthesis. Why didn't you adjust for SES? You did add a note on that analytical choice in the Discussion, but I am not convinced that this variables should be left out of analyses. What kind of SES data did you have? If you had information on income, education, neighborhood level socioeconomic data, I suggest you not only adjust for it, but also stratify the models by SES. You may inspect the covariance between noise and SES to make sure you are not overadjusting. You had data on hypertension, diabetes and BMI, so I would expect a sensitivity analysis in which you test those variables as potential effect modifiers. Admittedly, there are few diabetes cases, so the power may be insufficient, but the subsamples with hypertension and obesity are large enough for a subgroup analysis. In the Introduction, you talked about interactions between job strain/noise and obesity and smoking reported by other authors, so why not test those interactions in your study? Statistical analysis: I would like to see separate Cox regressions for fatal and non-fatal CHD and stroke. This may be helpful to draw conclusions as to the difference between morbidity and mortality risks, which is sometimes found in the field of environmental noise and CVD. Moreover, this will facilitate meta-analysts wishing to pool your study with others. Stratification of the Cox models by occupational group (white, blue, pink collar workers) would partially help address the lack of information on co-exposures and noise characteristics other than sound intensity. Maybe in some groups of workers the effect is larger? Results page 7: Report the lower limit of the exposure category < 75 dB and

	the upper limit of the > 85 dB category; also, the mean noise level in each of the three exposure categories. This will greatly facilitate deriving linear and non-linear trends in future meta-analyses on occupational noise and CHD/stroke, in which your study will probably be included. Table 2: You are correct that diabetes, obesity and hypertension are possibly mediators between noise and CVD. Thus the Risk factor adjusted model is very likely overadjusted. Table 3: You did not actually test interaction terms (noise□strain) to check whether they were statistically significant? I suggest you do so and report the p-values for the Wald test. Discussion page 9, second paragraph: Begin the limitations section on a new line. page 10, line 7: “attenuation” should be used “attenuating”. page 10, line 8: “limits”, not “limit”. page 10, line 11: “crude” would be better than “simple” page 10, line 12: Good that you acknowledge the possibility of the risk factors being mediators, but you should support this statement with relevant literature showing a link between occupational noise and BMI, diabetes, hypertension. page 10, line 16: Still, I would like to see at least a sensitivity analysis adjusting for SES and models stratified by SES. In general, your Discussion lacks the detailed description of previous studies, which you included in the Introduction. I would like you to elaborate in the Discussion on how your study and results compare to those of previous studies on noise and CVD. For example, some previous studies have also found no significant effect on stroke. Important limitations are not mentioned, but should have been: Hearing protector use, hearing status of participants, lack of data on co-exposures (dust, fumes, vibration!, which may be associated with CVD), no residential noise data. General comments: The structure of the manuscript is good, the arguments are clear and easy to follow. I am not a native speaker, but I think there are some missing commas and incorrect constructs here and there. e.g.,: “Regarding coronary heart disease and occupational exposure to noise the few available longitudinal studies seem to favour an association.”; “Exposure to work-place related stress is often classified according to the job-demand-control model (9), through the literature high strain, the combination of high demands and low control, has been linked to ill-health primarily coronary heart disease” “However, there seems to be interactions between…” “For the follow-up period there were 517 stroke events”

	"Concomitant exposure for high strain…"

VERSION 1 – AUTHOR RESPONSE

Gothenburg 8th of December 2017

Dear Editor,
Thank you for the opportunity to revise our manuscript entitled "A longitudinal study of occupational noise exposure and joint effects with job-strain and risk for coronary heart disease and stroke in Swedish men", manuscript ID bmjopen-2017-019160
We have revised the manuscript according the reviewers constructive suggestions.
In the letter below the comments from the editor and the reviewers are answered in italics.
The revisions in the manuscript has been marked in yellow.

Sincerely, Helena Eriksson, for the authors

Editorial Requests:

- Please amend the data sharing statement (page 12) to clarify how other researchers could access the dataset underlying the results (e.g. is it available upon request from the corresponding author?), or clarify whether there are any ethical or legal restrictions to accessing the dataset.
The data sharing statement has now been clarified, "Scientific cooperation around this study is possible by contacting the corresponding author".
Please add the relevant page numbers from the manuscript next to the items in the second half of the STROBE checklist (this has only been done for items 1-12 currently).
This has now been done, apologies for the missing information.

Quite extensive revisions has been made in the introduction and the discussion based on relevant improvement proposals from reviewer 2. For clarifying reasons, the category "Maybe noise peaks" has been added in the tables.

Reviewers' Comments to Author:

Reviewer: 1
Reviewer Name: Ferrario Marco
Institution and Country: Department of Medicine and Surgery. University of Insubria, Italy
Competing Interests: None declared

This is an interesting research on the joint effect of noise exposure and job strain in increasing the risk of CHD and Stroke. Not many papers addresses this topic and therefore it will be of sure interest for epidemiologists, occupational physicians and cardiologists, I presume. The study is a large prospective follow-up studies conducted by Swedish researchers on a Sweden sample. Both exposures were determined using job-exposure matrices. Results indicate a joint effect between the two exposures for CHD not for stroke. These finding corroborate previous researches' findings of the effects of the two independent exposures, adding more hints on the joint effect. The English is very good and the reader is facilitated in keep reading it.
There a few hints I wish to ask the authors to take into account, and that in my understanding may improve the paper.

1. I could not find any indication about the age range on this sample of 5753 working Swedish men. This may tell more about representativeness of the sample;
The men are born 1915-1925 and examined 1974-77 so the age range becomes 50-59 years which has now been added in the text.

2. Second para of Introduction: third row, I assume that the term “fatal” needs to be added. Please check;
The word fatal has been added, thank you.

3. The authors used the same abbreviation for the two job exposure-matrices (page 6). I suggest different acronyms.
The JEMs are now called the noise JEM and the psychosocial JEM.

4. I could not find a formalized statistical test for interaction. Was it done? On the same issue, looking at Table 3, probably the aggregation of the levels of exposures to noise below and above 75 dB(A), may help in testing the interactions. I also suggest to report the number of subjects and the number of events for each of the cells of Table 3, which may emphases the poor statistical power (which may improved a little with the proposed cell aggregation.
A statistical test for interaction was formerly done, we have now presented it in table 3. Medium and high noise have been aggregated, thank you for your very good advice. The number of events has now been added in table 3.

5. Finally, in Discussion first Para of Page 10, I would suggest to emphases the effects of high blood pressure and smoking, in addition to diabetes, which in my knowledge are stronger mediators of the relationships.
True, the sentence has now been removed. Different risk factors are now discussed.

Reviewer: 2
Reviewer Name: Angel Dzhambov
Institution and Country: Department of Hygiene and Ecomedicine, Faculty of Public Health, Medical University of Plovdiv, Bulgaria
Competing Interests: None declared

Comments below are also in the file attached.

This is a nice piece of research on a subject that is of interest to the occupational health community. Specifically, it adds to the limited body of evidence on occupational noise and stroke. Overall, I enjoyed reading the manuscript. Still, I have some comments that I would like to see addressed before it can be accepted for publication. I regard the necessary revision as “minor” despite the recommend additional analyses.

Abstract

line 20, Primary and secondary outcome measures: Add ICD codes if possible.
Good suggestion but it was not possible due to the restricted amount of words of the abstract.

line 22: Shouldn’t each word in “primary prevention study” be capitalized?
This has now been done.

line 47: I suggest adding “ischemic heart disease” to the list of keywords.
Thank you for your suggestion, IHD has now been added.

page 3, lines 5-6, “Exposure to noise is common in many workplaces, and health effects, especially hearing disorders have been investigated since decades.”: We sure know this, but a reference should be inserted at the end of the sentence.
A reference has now been added.

page 3, line 9: I disagree with the choice of references (№ 1 and 2). First of all, the meta-analysis of Skogstad et al. should be cited along with the erratum to it. You may also check my Letter to the editor concerning the analytical approach of Skogstad et al. There is reason to suspect that the random effects model in their meta-analysis overestimated the risk of hypertension (which is not to say that there isn’t a risk, rather the evidence from cohort studies isn’t there yet).
Thank you for your comment, the erratum has now been added.

Also, you should consider discussing the findings of the following systematic review, dealing with the risk of IHD attributed to occupational noise, in the next paragraph (lines 13-34):
Dzhambov AM, Dimitrova DD. Occupational noise and ischemic heart disease: A systematic review. Noise Health. 2016;18(83):167-77.
This reference has now been added.

The second and third paragraphs of the Introduction are a bit too detailed for my taste. I would expect to read about previous research and its strengths/limitations in the Discussion, not so early on in the paper. Thus I suggest that you shorten these paragraphs and briefly state what previous research indicated and what gaps still exist in the literature, and cover specific studies in the Discussion. Instead, the Introduction is a good place to briefly mention the epidemiology of CHD and stroke and the burden of disease associated with them, just to put your study in context. also, few notes on the mechanisms linking noise to CVD is worth mentioning.
Good point, the introduction has now been shortened and some of it has been moved to the discussion. Mechanisms and some statistics regarding the burden of disease has been added.

The third paragraph, where you talk about previous research on noise and stroke: You have missed two important references that should be mentioned (since there are very few studies on the topic to begin with). The first one reports both cross-sectional and longitudinal associations between noise and CVD, whereas the second one is cross-sectional, population-based study and representative of the US general population.
Gopinath B, Thiagalingam A, Teber E, Mitchell P. Exposure to workplace noise and the risk of cardiovascular disease events and mortality among older adults. Prev Med. 2011;53(6):390-4.

Dzhambov AM, Dimitrova DD, Tokmakova MP. Association between self-reported occupational noise and the prevalence of stroke: Secondary analysis of the National Health Interview Survey, 2014. Noise Control Engineering Journal. 2016;64(6):779-788.
These references have now been added.

page 4, line 12: I don’t see how the interaction between noise and smoking is relevant. ;
These sentences has now been changed and moved to the discussion, thank you for your comment.

Methods

page 4, lines 34-35: Consider putting “BMI is the weight in kilograms divided by the square of the body height in meters” in parenthesis.
This has now been done.

Why didn’t you adjust for SES? You did add a note on that analytical choice in the Discussion, but I am not convinced that this variables should be left out of analyses. What kind of SES data did you

have? If you had information on income, education, neighborhood level socioeconomic data, I suggest you not only adjust for it, but also stratify the models by SES. You may inspect the covariance between noise and SES to make sure you are not overadjusting...
Thank you for your suggestions. We don't have socioeconomic data and that information is now added in the manuscript. Based on occupational data we made a rough division of the cohort into blue collar and white collar workers. The covariate blue collar worker was not significant in the adjusted model. There is a correlation between noise and blue collar workers but the interaction term was negative, p=0,47 in the adjusted model. For stratified models, please see below*.

You had data on hypertension, diabetes and BMI, so I would expect a sensitivity analysis in which you test those variables as potential effect modifiers. Admittedly, there are few diabetes cases, so the power may be insufficient, but the subsamples with hypertension and obesity are large enough for a subgroup analysis:
We have analyzed the population without the subjects with hypertension and diabetes and it gives the same result, please see the added part in the results section. When excluding subjects with hypertension, high cholesterol, diabetes and BMI>30 it also gave similar results, not presented in the paper. However we have no data on developed hypertension which may have occurred during the follow up period.

In the Introduction, you talked about interactions between job strain/noise and obesity and smoking reported by other authors, so why not test those interactions in your study?
Besides high strain, we have analyzed potential interactions with all risk factors (except for age)and it was only hypertension that showed a significant interaction, and this interaction was negative, that is, the risk for CHD of noise exposure was higher among those who didn't have hypertension at baseline. This has not been added in the paper.

Statistical analysis: I would like to see separate Cox regressions for fatal and non-fatal CHD and stroke. This may be helpful to draw conclusions as to the difference between morbidity and mortality risks, which is sometimes found in the field of environmental noise and CVD. Moreover, this will facilitate meta-analysts wishing to pool your study with others.
Thank you for a very good suggestion, unfortunately it was not feasible within the frames of this study, we will consider this in forthcoming studies.

Stratification of the Cox models by occupational group (white, blue, pink collar workers) would partially help address the lack of information on co-exposures and noise characteristics other than sound intensity. Maybe in some groups of workers the effect is larger?
Thank you for your advice. The data set does not allow analyses of these three groups. *But crude analyzes of blue collar/white collar show that the effect is larger among blue collar workers but those are also the ones most exposed. Only 10-15% of the white collar workers are exposed to noise. The variable blue collar/white collar is not good enough in this study for publication.

Results

page 7: Report the lower limit of the exposure category < 75 dB and the upper limit of the > 85 dB category; also, the mean noise level in each of the three exposure categories. This will greatly facilitate deriving linear and non-linear trends in future meta-analyses on occupational noise and CHD/stroke, in which your study will probably be included.
We don't have access to individual exposure data, the subjects are classified according to the noise JEM and this JEM is divided into into three different levels, low; <75 dB(A), medium; 75-85 dB(A) and high; > 85 dB(A).

Table 2: You are correct that diabetes, obesity and hypertension are possibly mediators between noise and CVD. Thus the Risk factor adjusted model is very likely overadjusted.
Good point, we have presented both models.

Table 3: You did not actually test interaction terms (noise□strain) to check whether they were statistically significant? I suggest you do so and report the p-values for the Wald test.
Thank you for your suggestion, it has been done previously and we have now also presented it in table 3.

Discussion

page 9, second paragraph: Begin the limitations section on a new line.
This has now been done

page 10, line 7: “attenuation” should be used “attenuating”.
This has now been done.

page 10, line 8: “limits”, not “limit”.
This has now been done.

page 10, line 11: “crude” would be better than “simple”
This has now been done.

page 10, line 12: Good that you acknowledge the possibility of the risk factors being mediators, but you should support this statement with relevant literature showing a link between occupational noise and BMI, diabetes, hypertension.
Thank you for your advice. The link between occupational noise and hypertension is supported in the references in the manuscript. Regarding occupational noise and bmi and diabetes, a reference has been added in the introduction which supports a link between noise and metabolic effects.

page 10, line 16: Still, I would like to see at least a sensitivity analysis adjusting for SES and models stratified by SES.
Unfortunately we don’t have this data. When adjusting for the crude blue collar worker covariate, it was not significant in the adjusted model. We believe that the other risk factors indirectly also adjust for SES.

In general, your Discussion lacks the detailed description of previous studies, which you included in the Introduction. I would like you to elaborate in the Discussion on how your study and results compare to those of previous studies on noise and CVD. For example, some previous studies have also found no significant effect on stroke.
The discussion section has now been elaborated according to your proposal.

Important limitations are not mentioned, but should have been: Hearing protector use, hearing status of participants, lack of data on co-exposures (dust, fumes, vibration!, which may be associated with CVD), no residential noise data..
Most of the suggested limitations have now been added, thank you for your comment.
However, there are few studies regarding hearing status and the risk for CHD when noise exposure occurs, a hearing deficit could decrease or increase the risk for CHD. It is not clear whether hand and arm vibration exposure can increase the risk for CHD.

General comments: The structure of the manuscript is good, the arguments are clear and easy to follow. I am not a native speaker, but I think there are some missing commas and incorrect constructs here and there. e.g.,:
Thank you for your attention!

"Regarding coronary heart disease and occupational exposure to noise the few available longitudinal studies seem to favour an association.";
A comma has now been inserted.

"Exposure to work-place related stress is often classified according to the job-demand-control model (9), through the literature high strain, the combination of high demands and low control, has been linked to ill-health primarily coronary heart disease"
The sentence has now been changed.

"However, there seems to be interactions between…¨""
The word "However" has been removed.

"For the follow-up period there were 517 stroke events"
The sentence has been changed.

"Concomitant exposure for high strain…
A comma has been added"

VERSION 2 – REVIEW

REVIEWER	Angel Dzhambov Department of Hygiene and Ecomedicine, Faculty of Public Health, Medical University of Plovdiv
REVIEW RETURNED	12-Dec-2017

GENERAL COMMENTS	The authors did address most of my comments, but not all of them. They did provide convincing reasons as to why that was not possible, though. I am willing to accept that justification. In my view, the manuscript is a worthwhile read. Just some final polishing is needed, with no need for re-review on my side. Tables 2 and 3 are a little difficult to read, so consider presenting the data in a clearer fashion. Line 50, page 14: "The present study shows…." – too strong. "Suggests" would be better. In Discussion, first you say that the study has "high external validity", and then that "the study comprises only men which limits its external validity". I get what you mean, but you may soften a bit "high external validity". Some grammatical errors remain, e.g.,: "26500 suffered from a stroke" – "from"?! "All those clinical subtypes of stroke may have different risk factors" – "have"!

VERSION 2 – AUTHOR RESPONSE

Letter to editor
Gothenburg, 24th of January, 2018

Dear Editor,
Thank you again for the opportunity to revise our manuscript entitled “A longitudinal study of occupational noise exposure and joint effects with job-strain and risk for coronary heart disease and stroke in Swedish men”, manuscript ID bmjopen-2017-019160.R1.
We have revised the manuscript according to the suggestions.
In the letter below the comments from the editor and the reviewers are answered in italics.
The revisions in the manuscript has been marked in yellow.

Best regards, Helena Eriksson, for the authors

Editorial Requests:

- There are still some typographical/ grammatical errors in the manuscript (e.g. page 3: “Strenghts and limitations of this study” => “Strengths and limitations of this study”).
Our apologies, this has now been corrected.

Can you please carefully proofread the paper one more time? The quality of English needs improving in the following sentence in the discussion: “A sensitivity analysis was also performed, the cohort was analysed without the subjects with baseline hypertension and diabetes, a significantly increased risk with a positive trend remained for coronary heart disease.”
The sentence has been changed, thank you for your advice of improvement.

- Please improve the 'strengths and limitations' section on page 3. This section normally contains 4-5 bullet points. Each bullet point should be a full sentence. Can you briefly elaborate on why each point is a strength or limitation?
The “Strengths and limitations” section has now been elaborated.

Reviewer's Comments to Author:

Reviewer: 2
Reviewer Name: Angel Dzhambov
Institution and Country: Department of Hygiene and Ecomedicine, Faculty of Public Health, Medical University of Plovdiv, Bulgaria
Competing Interests: None declared

The authors did address most of my comments, but not all of them. They did provide convincing reasons as to why that was not possible, though. I am willing to accept that justification. In my view, the manuscript is a worthwhile read. Just some final polishing is needed, with no need for re-review on my side.

Tables 2 and 3 are a little difficult to read, so consider presenting the data in a clearer fashion.

Thank you for your advice. The tables have now adjusted. We have kept the amount of coronary events in table 3 due to advice from reviewer 1, in order to clarify the lack of statistical power, even though it increases the size of the table.

Line 50, page 14: “The present study shows….” – too strong. “Suggests” would be better.
“Shows” have now been changed to “suggests”.

In Discussion, first you say that the study has “high external validity”, and then that “the study comprises only men which limits its external validity”. I get what you mean, but you may soften a bit “high external validity”.
The word “high” has now been removed.

Some grammatical errors remain, e.g.,:

“26500 suffered from a stroke” – “from”?!
The sentence has been changed, thank you for your correction.

“All those clinical subtypes of stroke may have different risk factors” – “have”!
The sentence has been changed.

“concomitant exposure for high strain further increased the risk of CHD.” – “to”, not “for”
Thank you for your correction, the word “for” has been changed.